

Digitalis use in acute myocardial infarction: current concepts

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Summary: Digitalis is one of the oldest and most commonly prescribed medications. There has been continuing controversy regarding its use in acute myocardial infarction. Recent information from animal experiments and clinical investigation serves as a guide for its appropriate use in this situation. When it is used appropriately and judiciously there is no increase in toxicity or cardiac arrhythmias. In fact, there is benefit to the patient who has a failing myocardium associated with acute myocardial infarction.

Résumé: La digitale dans l'infarctus aigu du myocarde: les concepts récents

La digitale est sans doute un des plus vieux médicaments et aussi le plus couramment prescrit. C'est cependant le produit dont l'emploi dans l'infarctus aigu du myocarde a été le plus longtemps controversé. Les données recueillies à partir d'expériences chez l'animal et d'observations cliniques peuvent servir de guide au clinicien qui cherche à l'employer judicieusement dans cette pathologie. En effet, employée à bon escient, la digitale ne risque pas d'augmenter la toxicité ou l'arythmie cardiaque. En fait, le malade dont le myocarde est défaillant et qui présente un infarctus du myocarde concomitant retire du profit de la digitalisation.

Although digitalis therapy for acute myocardial infarction has been advocated since Herrick's¹ original proposal for such use in 1912, considerable controversy concerning its value and indications still exists. There traditionally

has been some hesitancy on the part of clinicians to use digitalis in this situation. Perhaps this is based partly on the impression that digitalis may be less efficacious in treating heart failure due to acute myocardial infarction than in treating that due to chronic coronary artery disease, and partly on the fear that the acutely ischemic myocardium, which often spontaneously manifests ventricular irritability, may be unusually sensitive to digitalis-induced arrhythmias. The appropriate use of this drug should be guided by sound scientific studies, not by unsupported opinions, speculations or clinical impressions.

Recently a body of substantial information^{2,3} has emerged regarding the mechanism of action and pharmacology of cardiac glycosides, which can guide the physician in the use of this important drug in the patient with acute myocardial infarction.^{4,5} This article summarizes several recent extensive reviews and experimental studies, and focuses on practical applications for the practising physician.

Objections: fact or fiction?

There are several common objections to the use of digitalis in patients with acute myocardial infarction.

Increased risk of arrhythmias

The belief that the injured myocardium is more susceptible to toxic arrhythmias originates from animal studies that have consistently shown a reduction of 24 to 33% in the digitalis dose required to induce ventricular tachyarrhythmias after acute myocardial infarction.^{6,7} Although this occurs on the first day, there is an increased tolerance towards normal from 48 hours to seven days later. This may be a result of failure by infarcted muscle to metabolize or absorb the digitalis, variation in uptake, and differences in drug concentration

in adjacent areas of heart muscle. Recovery times may be altered and subsequently predispose to re-entrant rhythm disturbances.³ Although inotropic agents, including ouabain, may increase the severity and the extent of injury in the nonfailing heart,⁸ in the presence of heart failure ouabain actually decreases both myocardial oxygen consumption and the area of ischemic injury by reducing heart size.

There are no valid clinical studies that prove that this digitalis danger exists in human myocardial infarction. Digitalis obtained a bad reputation from early animal studies that showed enhanced ectopic activity, but only at toxic doses,^{9,10} the comparable human dose being 17.5 mg digoxin.

Schemm¹¹ gave digitalis to 265 patients with myocardial infarction and reported a total mortality of 10%; a control group of 286 not receiving digitalis had a 16% mortality. In a prospective series of 100 patients with myocardial infarction Askey¹² gave digitoxin to alternate patients. The incidence of sudden death and serious complicating arrhythmias was comparable in the two groups. Judicious use of this drug does not produce undesirable toxic effects. Lown *et al*¹³ have uniquely demonstrated that the majority of patients with acute myocardial infarction can safely be treated with digitalis. Fifty-four patients in a coronary care unit were given acetylstrophanthidin in 0.1- to 0.2-mg increments within 48 hours of admission. The test was completed when a total of 1.0 mg had been administered, or when clinical or electrocardiographic changes indicated intoxication. Eighty-nine percent of the 54 patients easily tolerated the full dose of intravenous acetylstrophanthidin, which is equivalent to 1.5 mg of digoxin.

Any increase in the susceptibility to digitalis toxicity or irritability may relate to both the dose employed and the severity of complications, e.g. hypoxia,

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TOXICITY: No reports of fatal overdosage in man. No adverse effects from high dosage in chronic animal studies.

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Increased risk of myocardial rupture

Since glycosides increase the contractile force developed by the myocardium it is speculated that digitalis might lead to an increase in the risk of myocardial rupture in acute infarction.¹⁴ Although rupture of the heart occurs in 8% of fatal acute myocardial infarctions, the incidence is actually the same in patients receiving digitalis.¹⁵

Vasoconstrictive effect on coronary arteries

The results of studies on the anesthetized animal have been inconsistent, since they may be modified by the effects of anesthesia and surgical manipulation.⁴ Nevertheless, ouabain does produce coronary vasoconstriction and increased coronary vascular resistance, possibly as a vagal effect. Therefore, caution is advised in rapid injection of a bolus of cardiac glycosides in patients with acute infarction. The effect on patients with coronary arteriosclerosis has not yet been demonstrated.

Increased total systemic vascular resistance

In both conscious laboratory animals and in humans, regardless of the state of cardiac compensation, large doses of cardiac glycosides given intravenously can produce increases in systemic resistance and systemic blood pressure.¹⁶ Since "afterload" is an important determinant of myocardial oxygen consumption and stroke output, sudden increases in blood pressure may actually be deleterious. In the study of Lown *et al*¹³ acetylthioflavine caused an increase in blood pressure in 32 of 54 patients (59%), the increase exceeding 20 mm Hg in 16 of the 32 cases. Caution is advised in the rapid intravenous administration of digoxin, and in the use of rapidly acting glycosides such as acetylthioflavine or ouabain. Indeed, the early pressor effect of an intravenous glycoside may initially be harmful to some patients with cardiogenic shock. The vasoconstrictive effect of digitalis may precede the inotropic effect.¹⁷

Effect on myocardial performance

Previous studies have shown no significant improvement in cardiac output within two hours after the administration of intravenous digoxin to patients with acute myocardial infarction.^{18,19} Although Hodges *et al*¹⁹ state that digitalis is of limited value during the early stages of acute infarction, they continued giving the drug and the "signs of left ventricular failure cleared in all patients before discharge". However,

the studies showing unaltered cardiac output are not necessarily evidence that digitalis fails to improve ventricular performance, since the cardiac output and the heart's contractile state are not synonymous, nor are they related to each other in a simple manner.²⁰ The heart's function as a pump may be unaltered, but there is improvement in myocardial contractility with the administration of a cardiac glycoside during acute infarction, as shown by Rahimtoola *et al*.²¹ Although they found no alteration in cardiac index, heart rate or mean arterial pressure after intravenous ouabain, they observed the following improvements: decrease in left ventricular end-diastolic pressure; shortening of pre-ejection period; and increase in left ventricular work, peak first derivative of left ventricular pressure (dp/dt), and maximum velocity of contractile-element shortening (Vmax).

Therefore, more sensitive techniques that assess the heart's contractile properties do show improvement in left ventricular function when digitalis is given in acute myocardial infarction.

Indications

Supraventricular arrhythmias

Supraventricular arrhythmias occur in approximately 25% of acute myocardial infarctions,²² and often develop in patients with ventricular failure. Atrial fibrillation, flutter and tachycardia are universally accepted as indications for digitalis therapy. Since frequent premature atrial contractions often are a prelude to atrial fibrillation, digitalis is recommended when they appear.

Heart failure

The late Charles Friedberg²³ recommended the use of digitalis in acute myocardial infarction only when there is persistent pulmonary edema or heart failure not controlled by bed rest, opiates and oxygen. The criteria proposed by Logue and Hurst²⁴ are somewhat broader and include the presence of gallop sounds, pulmonary rales, radiographic evidence of interstitial edema, and an unexplained sinus rate exceeding 110 beats per minute. Lown and co-workers²⁵ agree with the latter recommendations, but found that 22% of patients with congestive symptoms demonstrated an inadequate response to digitalis and subsequently required diuretics. An alternative approach is advocated by Swan and associates²⁵ who recommend using digoxin for patients with heart failure who do not respond adequately to diuretics. In any case, one should watch for subtle manifestations of cardiac failure, such as pul-

monary edema without cardiomegaly,²⁶ or radiologic evidence of pulmonary congestion without rales.²⁷

Although several respected medical authorities have alternative therapeutic philosophies, each mode of treatment may be equally efficacious. I usually give diuretic therapy a 24- to 48-hour trial, and then prescribe digoxin if heart failure persists.

Appropriate use

William Withering²⁴ thought it was necessary to produce nausea to achieve a therapeutic effect with foxglove. However, he subsequently observed that the diuretic effect preceded the toxic effect on the stomach, the pulse or the bowels. Similarly, in the current era no attempt should be made to push the digitalis dosage until minor or major toxic symptoms develop. Cardiac glycosides can and should be used safely in acute myocardial infarction, but in lower doses than traditionally recommended, for the following reasons:

1. Although clinical evidence is lacking that patients with acute myocardial infarction are prone to develop digitalis-induced arrhythmias, the experimental evidence from animals indicates that the average intoxicating dose after infarction may be one third less.^{6,7} This may indicate that infarcted muscle does not utilize the drug and that there is lack of homogeneity of uptake, so less drug is actually required by the heart.
2. The myocardium shows improved contractility and a positive inotropic effect with low doses of digoxin, and "full digitalization", or a "digitalizing" dose, is not necessary for a physiologic or clinical effect.^{28,29} A little is better than nothing, and definitely better than a lot. *Primum non nocere*. Ratshin *et al*³⁰ noted small increases in cardiac index and stroke work as well as reduced left ventricular end-diastolic pressure 30 to 45 minutes after administration of 0.5 to 0.75 mg of intravenous digoxin. Other work has demonstrated that two thirds of the usual ouabain dose given to patients with acute myocardial infarction causes significant improvement in impaired left ventricular function as manifested by increased dp/dt and Vmax.³¹ Thus, the concept of "digitalization", which implies that the myocardium has to be saturated for an effect to be produced, can be discarded.
3. With an acute myocardial infarction the surrounding and surviving myocardium is ischemic. Systemic hypoxia is common in patients with heart failure or myocardial infarction because of impaired gas ex-

change and ventilation-perfusion imbalance.⁴ In addition there is an area of muscle surrounding the infarct which is a borderline or "twilight" zone.³¹ Although the ischemic myocardium shows improved contractility with digitalis,³² there is increased irritability with hypoxia. Any hypercapnia or acidosis may further sensitize the heart to arrhythmias.³³ Before giving digitalis the acidosis, hypoxemia and metabolic imbalances should be corrected.

4. Mild renal decompensation is common in acute myocardial infarction and is due to heart failure, over-vigorous diuretic therapy producing decreased plasma volume, and the coexistence of endogenous renal disease. Since renal function directly affects serum digoxin metabolism, the dose of digoxin must be titrated accordingly.²
5. Potassium balance is frequently disturbed subsequent to diuretic therapy, inadequate supplementation, nausea and vomiting, and secondary aldosteronism due to heart failure. This may increase the risk of digitalis toxicity.
6. Because of smaller body size and decreased renal function, the elderly patient should be given smaller loading and maintenance doses.³⁴
7. Digitalis may aggravate atrioventricular block.

If digitalis is given, it is best for the individual physician to prescribe the preparation with which he is most familiar. Even in congestive heart failure, therapeutic blood levels can easily be achieved with oral digoxin.¹ However, the clinical condition often demands that the drug be given parenterally. More reliable blood concentrations can be attained with the oral or the intravenous route than with the intramuscular.² In addition, since the latter route is painful and its use may elevate levels of serum muscle enzymes it should be discouraged. For oral use the average "digitalizing" dose of digoxin is 1.5 mg, and the intravenous dose is 0.75 to 1.0 mg.^{2,3,24}

Special caution should be taken when any of the following are present: second or third degree atrioventricular block, sinus bradycardia, atrioventricular dissociation, ventricular tachycardia and hypokalemia. Myocardial oxygen consumption and the area of injury are increased by digitalis in the nonfailing heart.⁸ There is no role for the prophylactic use of digitalis in the uncomplicated myocardial infarction. *Primum non nocere*.

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